Cow's milk allergy in children: adherence to a therapeutic elimination diet and reintroduction of milk into the diet

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Running title

Adherence to an elimination diet

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Abstract

Background/Objectives: The basic treatment of cow's milk allergy (CMA) is the elimination of all cow's milk proteins (CMP) from the diet. The present study aimed at characterising the diet of children with a diagnosis of CMA, to assess the degree of adherence to the elimination diet and to evaluate factors associated with the adherence and age of recovery.

Subjects/Methods: From a birth cohort study, food records of 267 children with diagnosed CMA were studied to define how strictly the elimination diet was adhered to. Subsequent food records were studied to assess the age at reintroduction of milk products in the child's diet.

Results: The families adhered to the elimination diet of the child with extreme accuracy in 85% of the cases. Older and monosensitised children had more often small amounts of CMP in their diet, possibly due the absence of nutritional information by a dietitian/nutritionist. Adherence to the diet was not related to any other sociodemographic factor studied nor to the age at reintroduction of milk products into the diet.

Conclusions: The therapeutic elimination diet of children with a diagnosed CMA was well adhered to. Low intakes of vitamin D, calcium and riboflavin are of concern in children who follow or have followed a cow's milk-free diet.

Key words

adherence; child, preschool; cow's milk allergy; elimination diet; infant

Offprints not available

INTRODUCTION

Special infant formulas are used instead of cow's milk -based formulas in the diet of milk-allergic infants if the infant is not fully breastfed. If cow's milk allergy (CMA) is diagnosed by a physician, children up to the age of 2 years receive reimbursement for their costs from the Finnish Social Insurance Institution, offering a great opportunity to study CMA. The costs of the special infant formulas are substantial to the society, but management will not be fully effective if the cow's milk free diet is not followed properly.

The risks of a cow's milk-free diet are well documented (Hidvegi *et al*. 2003, Jensen *et al*. 2004, Rockell *et al*. 2005). The diet should be balanced, providing adequate amounts of calcium and vitamin D, either by using the correct substitute foods or by supplementation (Grimshaw 2006, Vandenplas *et al*. 2007).

By asking parents about the level of the elimination, adherence to a therapeutic elimination diet in children has been assessed in three previous studies (Vlieg-Boerstra *et al*. 2006, Eggesbo *et al*. 2001, Allen *et al.* 2009). These studies suggest problems in adhering to an elimination diet, whether warranted or not.

So far no study has objectively assessed the adherence to a therapeutic elimination diet in children with food allergy, such as in the form of food records. The aims of the present study were to analyse the diet of children following a cow's milk protein (CMP) -free diet, to study the reintroduction of milk products into children's diets, and to evaluate factors associated with the adherence and age of development of tolerance.

SUBJECTS AND METHODS

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study is a multidisciplinary prospective population-based cohort study (Kupila *et al*. 2001). All newborns from the catchment areas of three university hospitals in Finland (Turku, Oulu, and Tampere) are screened for HLA-conferred susceptibility to type 1 diabetes from cord blood samples after parental informed consent. Infants with high and moderate risk for type 1 diabetes (15% of those screened) are invited to participate in the study, excluding children with severe congenital abnormalities or diseases, or whose parents are of non-Caucasian origin or do not understand Finnish, Swedish or English. The DIPP Nutrition study is performed in the Oulu and Tampere University hospitals among children born since October 1996. The local Ethical Committees have approved the study. All families have given their written informed consent to participate in the DIPP study.

The presence of special infant formula reimbursement was checked from the Finnish Social Insurance Institution for children in the DIPP Nutrition Study for whom a personal identification code was known to the study (n = 6412). According to clinical practice guidelines, the diagnosis is based on improvement of symptoms on an elimination diet, followed by a positive food challenge outcome or, in rare cases, on a high IgE level and improvement of symptoms on an elimination diet (Finnish Paediatric Association 2004). For those 398 (6.2%) children who received the reimbursement, information on the month and year of the beginning of the reimbursement (in other words a diagnosed CMA) was obtained.

Three-day food records, completed blindly to the purpose of the present study, were collected at the ages of 3 and 6 months, and 1, 2 and 3 years (Kyttälä *et al*. 2010). Parents were given written and oral instructions on how to record everything the child ate and drank during the recording period. Separate food record forms, which also comprised questions e.g. about the

origin of the food, were provided for the day care. Three consecutive food record dates were assigned to the family in advance and contained two week and one week end day. Examples were given on how to report food consumption with household or weighed measures. Vitamin and mineral supplement usage was also recorded. Food picture booklets were used to help the estimation of portion sizes (Paturi *et al.* 2006, Ovaskainen *et al.* 2008).

Trained research nurses checked the food records with the families, and nutrition researchers entered all the food consumption data using an in-house software into the Finnish national food composition databank Fineli (National Institute for Health and Welfare, Nutrition Unit 2009). Food consumption and nutrient intakes, as well as the amount of CMP were calculated as average daily intake using the database. When calculating the amount of CMP, its quantity in all foods was taken into account, except for sausages, fat spreads and commercial biscuits. However, these were taken into account when classifying adherence. The recording of food records was checked for food consumption and nutrient intakes, and for sources of CMP, to ensure valid recording and the validity of the databank used.

Information on special diets was collected at the ages of 3 and 6 months, and at 1 and 2 years by open questions and at the age of 3 years by a structured, validated questionnaire (Tuokkola *et al*. 2008). Parental reports of food allergies were double-entered to ensure valid recording.

To study the adherence to the cow's milk elimination diet, the next food record within 6 months from receiving the special reimbursement was analysed for the level of the elimination. Food records were classified as containing milk products, containing hidden or small amounts of CMP, containing no CMP, and containing no obvious sources of CMP but having recipes for which there is some uncertainty on whether they contain CMP or not. The latter consists of food items from small local bakeries and meat product manufacturers for which the detailed composition could not be traced, and if a commercial product name was not identified in the food record. To study the reintroduction of milk products into the diet,

subsequent food records either up to a food record containing milk products, up to the latest food record or up to 3 years of age were further analysed.

Background information (parental age and education, the number of siblings) was collected at the time of recruitment. Information on parental smoking, former childbirths of the mother, and place of residence were obtained from the Finnish Medical Birth Registry.

SPSS software package 15.0 (SPSS Inc, Chicago, IL, 2006) and R 2.7.0 (R Development Core Team, 2008) were used for statistical analyses. Multinomial logistic regression was applied to study the associations of adherence to the therapeutic elimination diet with background factors. Cox proportional hazards model with an accommodation to interval censored data was used to identify the factors associated with the age of recovery.

RESULTS

The adherence to the cow's milk elimination diet was studied in 267 children (67% of those with the reimbursement), from whom a food record within 6 months from receiving the reimbursement was available. Of these 267 families, 226 had followed the therapeutic elimination diet extremely accurately (Table 1). Small amounts of CMP were seen in the diet of 14 children, but only eight had used actual milk products. In addition, in 19 children there were no obvious sources of CMP, but food records included some recipes or foodstuffs for which there is uncertainty of them containing CMP. The parents of three children reported being in a process of an oral challenge test with milk and these children were classified adherent.

Those eight children whose parents reported consumption of milk products had a mean intake of 350 g (range 76 g – 1136 g) of milk products during the 3 days. The amount of CMP ranged from 2.0 g to 36.5 g, with a mean intake of 8.5 g and median intake of 4.0 g of CMP. Those 14 children whose parents reported consumption of foodstuffs classified as containing small amounts of CMP had a mean intake of 6.8 g (range 0.0 g – 42.7 g) of milk products during the 3 days. The amount of CMP from these foods ranged from 0.0 g to 9.1 g, with a mean intake of 1.0 g and median intake of 0.02 g.

Four of the eight children who had used milk products had also used special infant formulas (Table 2). Mean intakes of calcium were below recommendations, but due to supplementation, mean intakes of vitamin D were sufficient (Table 3). In addition, the intakes of riboflavin and calcium were especially low in food records containing neither milk products nor a special infant formula (n = 89, data not shown).

Of the children with CMA, 59% were boys. The median duration of overall breastfeeding was 6 months and that of exclusive breastfeeding 2 months, and the reimbursement for the

special infant formula was received at a median age of 5 months. Parental age and education, the number of siblings, gender, the duration of breastfeeding, urbanity of the place of living, and the study centre were not associated with the adherence to the therapeutic elimination diet. An older age of the child, as well as lack of other food allergies besides CMA, increased the risk of having small amounts of CMP in the diet ($p < 0.001$ for both; adjusted for maternal age and education, number of siblings, sex, duration of breastfeeding, and study centre).

The presence of CMP in the diet within 6 months from receiving the reimbursement did not predict the age at reintroduction of CMP in the diet, nor did place of residence, sex, or parental age or education level. The children of smoking mothers were reintroduced milk products at a younger age than the children of non-smoking mothers, when adjusted for the age and sex of the child, adherence to the elimination diet, maternal education and age, the duration of breastfeeding, and study centre ($p < 0.05$).

To study the reintroduction of milk products into the child's diet, subsequent food records were studied in children who initially had adhered to a CMP-free diet. Of the 259 children who had followed the CMP-free diet, subsequent food records were available from 215 children, who were observed further. Altogether 120 children had begun to use milk products during follow-up (Fig 1). At the age of 3 years, 55 children were still avoiding milk; 40 children had left the study before the age of 3 years and had not begun to use milk products up to the last available study point.

The main milk products used after the period of milk elimination were milk (87% of children), cheese (67% of children), and yoghurt (45% of children). However, amounts of milk products used were small, and only 17% of children consumed three glasses of milk, 23% used at least two slices of cheese and 15% used at least 1 dl of yoghurt daily.

DISCUSSION

The therapeutic elimination diet in children with a diagnosed CMA was very well adhered to. As many as 85% of the families followed the diet extremely accurately, and an additional 7% had no obvious sources of CMP, but food records contained some foodstuffs with an unknown recipe. Small amounts of CMP were observed in the diet of 5% of the children, and only 3% had used milk products. Those who had consumed small amounts of CMP were older and more often monosensitised, but otherwise sociodemographic factors were not associated with the adherence. By the age of 3 years about a half of the children had begun to use milk products and a quarter of the children were still avoiding CMP. Initial adherence to the elimination diet was not associated with the age of ending the CMP-free diet.

Major strengths of the study are the large population studied, and that food records were collected for purposes other than to study the adherence to a CMP elimination diet, diminishing embellishment. On the other hand, there were some inexact elements in some food records: imprecise recording of food items consumed, or not having information detailed enough on products such as from small bakeries and meat product manufacturers dating years back. However, for 93% of the children consumption of foods containing even the smallest amounts of CMP could be accurately evaluated.

The limitations of the study lie within possible problems in diagnostics, in not knowing the children's' symptoms, in the cumbrousness of the database used for the purpose of the present study, and in the rather long intervals in which the diets of the children could be studied. Relying on registry data for the diagnosis of CMA may, in part, explain the rather high percentage (6.2%) of children with a diagnosed CMA, despite the national guidelines for the diagnosis (Finnish Paediatric Association 2004). In our previous validation study, we found that not all children underwent an oral challenge test before receiving the diagnosis, so overdiagnosis is possible (Tuokkola *et al.* 2008). In addition, the strong research in the field

of food allergies in both university hospitals where the cohort was gathered may increase awareness of the disease and the tendency to seek for a diagnosis.

Two of the eight children with milk products in their diet had reportedly used a special infant formula only for 2 weeks, and these children had likely received the reimbursement on false grounds. There were four children, who consumed both a special infant formula, and some milk products. The costs of the use of special infant formulas to society are considerable, and unnecessary use should be avoided. Why eight children had consumed CMP-containing porridges, gruels and other ready-to-use baby foods, is not known.

Compared with previous studies addressing the adherence to a therapeutic elimination diet in children with food hypersensitivities, in which approximately one to two thirds of the populations were fully adherent, our study subjects show a much higher adherence (Vlieg-Boerstra *et al*. 2006, Eggesbo *et al*. 2001, Allen *et al*. 2009). The reasons for this are most likely due to methodological differences (questionnaires vs. food records), as well as differences in the populations studied (age groups, the basis for diagnosis, and food allergies). Adherence to dietary treatment of celiac disease shows variation between 30% to 95%, depending on the methods used and the age of the children; no studies report adherence in an age group comparable to the present cohort of children under the age of 3 years (Hommel *et al*. 2008). Our results are based on 3-day food records, and we have no knowledge on the diets beyond those days, which is a limitation compared with the studies using questionnaires in defining the level of adherence. However, food records collected blindly to the purpose of the present study are presumed to give an otherwise reliable answer. The total number of days examined in our study amounts to 781. One particular reason for the high level of adherence in our study population could be the requirement for the food industry to mention CMP on food labels, making it easier to follow the elimination diet. Being aware of an increased genetic risk for type 1 diabetes may also increase the adherence to a dietary treatment.

In Finland those children who are allergic only to CMP do not often see a nutritionist, which may explain the association between monosensitisation and consuming CMP hidden in foodstuffs. The ingestion of these foods may be considered as accidents or as ignorance, and could be counteracted by dietary counselling, if necessary. Unfortunately, information on visits to a nutritionist was not available to us. On the other hand, monosensitised children may have a milder form of the disease, and actually tolerate small amounts of CMP. As in the study by Eggesbo *et al.*(2001), maternal age and education were not associated with adherence to the elimination diet.

When studying the introduction of milk into the child's diet, our main hypothesis was that consuming small amounts of CMP would lead to a quicker recovery from CMA and reintroduction of milk products into the child's diet. However, in this group of children this was not the case; initial adherence was not associated with the age at reintroduction of milk products. Vlieg-Boerstra *et al.* (2006) reported similar findings: in their study unintentional consumption of an allergenic food did not predict the outcome of an oral challenge. Likewise, in the study by Allen *et al.* (2009), adherence to an egg elimination diet did not predict the outcome of a challenge. In our study, the only background factor associated with an earlier introduction of milk products was maternal smoking during pregnancy. We assume that this association does not truly reflect a quicker recovery from CMA, but rather the motivation for following the prescribed diet. The question of whether ingesting small amounts of CMP in a home setting would induce tolerance should be addressed with more frequent follow-up. We could not find any such associations, but this could be due to the lengthy intervals of studying the inclusion of CMP into the diet. The age at recovery from CMA is earlier in the present study than that previously reported by Skripak *et al.* (2007), who studied children with an IgE-mediated CMA. The recovery rate in the present study follows more closely that presented by Vanto *et al.* (2004), who also included both IgE-mediated and non-IgE-

mediated CMA in his study. The recovery rate may also be affected by the fact that the diagnosis is done in clinical practice and not by the researchers in the present study.

Children following a CMP-free diet require attention to fulfil their needs for calcium, vitamin D and riboflavin. In addition, children recovered from CMA consume less milk products than children on average do (Kyttälä *et al*. 2010); the concern of receiving enough calcium and vitamin D is still present after the inclusion of milk into the diet.

In summary, adherence to a therapeutic elimination diet of children with diagnosed CMA was extremely good. Monosensitisation and older age are associated with sloppier adherence, possibly due the absence of nutritional information by a dietitian/nutritionist. Intakes of calcium, riboflavin and vitamin D are of concern in children who follow or have followed a CMP-free diet. This study does not show evidence that small amounts of CMP would lead to a quicker recovery from CMA in a real-life setting.

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Conflict of interest statement

The authors declare no conflict of interest.

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Table 1. Adherence to cow's milk protein (CMP) elimination diet within 6 months after the diagnosis of cow's milk allergy, n = 267

Child has consumed	n	%
No CMP	226	85.0
Some uncertain food items without obvious sources of CMP[1]	19	7.1
Hidden or small amounts of CMP[2]	14	4.9
Milk or milk products[3]	8	3.0

[1]Meat and bakery products for which a recipe was not known, or if a commercial name of a meat or bakery product or a ready-to-use baby food was not specified

[2]CMP in food items such as industrial baby-foods, bakery and meat products, or fat spreads containing CMP as an ingredient, cookies with milk chocolate, or a few cheese puffs.

[3]Milk products used were cheese, ice cream, infant formulas, as well as milk-containing infant porridges, and gruels.

Table 2. Adherence to the cow's milk elimination diet: milks and special infant formulas that were used during the 3 study days[1] within 6 months from receiving a diagnosis of cow's milk allergy by age (each child may be accounted for more than once if having consumed more than one type of milk or drink; number of children = 264).

	3 months n = 48	6 months n = 106	1 year n = 106	2 years n = 4
Breast milk	26	41	17	0
Amino-acid formula	6	26	25	0
Hydrolysed formula	22	48	47	1
Soy formula	3	7	24	2
Cow's milk formula[2]	1	6	1	0
Cow's milk[2]	0	0	1	0
Soydrink	0	0	6	0
Oatdrink	0	0	2	1
Ricedrink	0	0	2	1

[1]Those who had reported an ongoing challenge test with cow's milk are not included.

[2]The reason for the consumption of cow's milk formula and cow's milk is not known.

Table 3. Adherence to the cow's milk elimination diet: mean (SD) intakes of energy and certain nutrients, intake from foods and supplements together, of non-breastfed children by age[1]

		3 months (n = 22)	6 months (n = 67)	1 year (n = 89)	2 years (n = 4)
Energy kJ[2]		2430 (277)	2800 (554)	3910 (760)	4370 (325)
Protein	% of energy	10.2 (0.8)	10.2 (1.6)	12.2 (2.7)	12.1 (2.9)
Carbohydrates	% of energy	40.7 (5.3)	50.8 (7.4)	55.0 (6.7)	56.1 (5.5)
Fat	% of energy	49.0 (5.1)	38.7 (7.0)	32.4 (7.2)	31.2 (7.7)
Calcium[3]	mg	467 (60)	430 (130)	473 (191)	780 (248)
Vitamin D[4]	µg	14.7 (4.2)	14.1 (4.0)	13.3 (4.2)	12.3 (10.7)
Riboflavin[5]	mg	0.84 (0.26)	0.74 (0.25)	0.81 (0.38)	1.14 (0.55)

[1]within 6 months from receiving a reimbursement of the special infant formulas

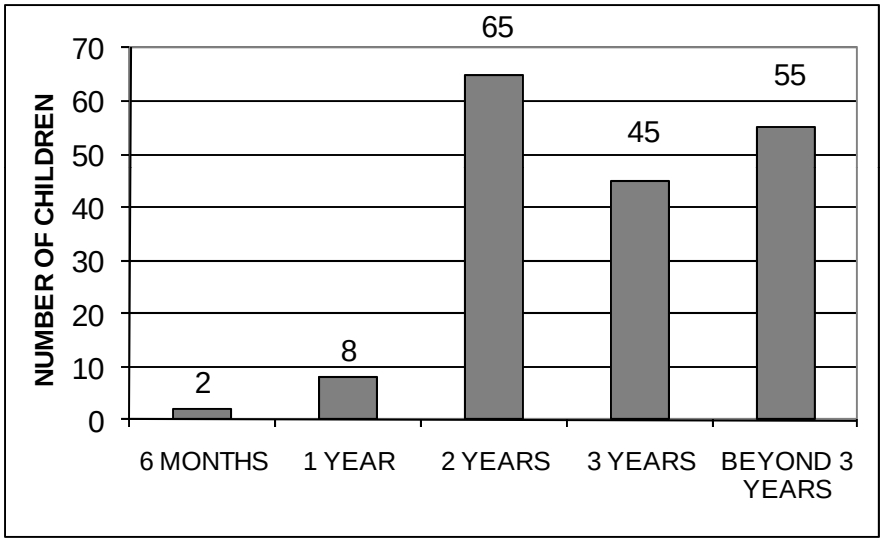
[2]Estimated needs for energy at 3 months 2100 kJ for girls and 2200 kJ for boys, at 6 months for 2600 kJ for girls and 2700 kJ for boys, at 1 year 3400 kJ for girls and 3700 kJ for boys, and at the age of 2 years 4400 kJ for girls and 4700 kJ for boys.

[3]Recommended intake 540 mg for 6 – 11 months of age, 600 mg for 1-2 years of age

[4]Recommended intake 10 µg for 6 – 23 months of age, 7.5 µg for 2 years of age

[5]Recommended intake 0.5 mg for 6 – 11 months of age, 0.6 mg for 12-23 months of age, and 0.7 mg for 2 years of age

Figure 1. Number of children, in whom cow's milk was reintroduced into the diet for the first time after the diagnosis of cow's milk allergy. In addition, 40 children had dropped out from the study before the age of 3 years, and had not reintroduced milk products into the diet at the last available food record.


NUMBER OF CHILDREN
70
60
50
40
30
20
10
0
2
8
65
45
55
6 MONTHS
1 YEAR
2 YEARS
3 YEARS
BEYOND 3 YEARS